Lactate measurement: arterial versus capillary blood

June 2017

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Summary

This article reviews the results of recent clinical studies on measuring lactate in arterial versus capillary blood. While arterial blood is the gold standard sample for lactate measurement on blood gas and other point-of-care analyzers, capillary blood is an alternative sample for lactate measurement on hand-held devices.

However, based on evidence from studies, the article concludes that capillary blood lactate measurement should be used with caution and reserved for clinical settings where rapid arterial lactate measurement is not available.

Lactate is the end product of the metabolic process of glucose utilization, known as anaerobic glycolysis, which occurs in the cytosol of all cells. In well-oxygenated tissues this lactate is metabolized further, but if tissues are inadequately oxygenated, lactate accumulates locally and blood concentration rises.

As a sensitive but non-specific blood marker of tissue hypoxia, point-of-care (POC) lactate measurement has long-established clinical utility in the early assessment and monitoring of acutely/critically ill patients and major trauma victims in emergency room and intensive care units.

Arterial blood is the preferred gold standard sample for lactate measurement that is used to determine lactate by well-validated methods on blood gas and other point-of-care analyzers, as well as those sited in the central laboratory. Capillary blood, which is more easily obtained (by finger or earlobe puncture), is an alternative sample employed for lactate determination by a range of hand-held lactate measuring devices.

	Median lactate (range)	Mean difference/bias arterial minus capillary	95 % limits of agreement from Bland-Altman plot
Arterial blood (n=193)	1.6 mmol/L (0.5-10.9)	−0.08 mmol/L	−0.77 to 0.61 mmol/L
Capillary blood (n=193)	1.6 mmol/L (0.7-10.6)		

TABLE I: Capillary vs. arterial lactate concentration (193 pairs) determined by blood gas analyzer

Does capillary lactate concentration determined by these hand-held devices accurately reflect arterial lactate concentration determined by established point-of-care/central laboratory analyzers? The purpose of this article is to review results of recent clinical studies that have addressed this question.

Evidence of agreement between arterial lactate and capillary lactate

Correlation and level of agreement between capillary and arterial blood lactate concentration is obviously best investigated by using a well-validated lactate methodology to measure lactate in simultaneously sampled arterial and capillary blood.

This was the approach adopted by Fauchere et al [1] who studied 25 sick neonates in intensive care, all requiring an indwelling umbilical arterial catheter. Arterial and simultaneously collected capillary blood was sampled for lactate measurement from these sick babies on multiple (median 5, range 2-20) occasions.

Lactate concentration of all samples was determined using the same blood gas analyzer located in the intensive care unit. A total of 193 paired (arterial and capillary) lactate results were generated for statistical analysis (linear regression and Bland-Altman plot). Near-perfect correlation (r=0.98) and excellent level of agreement across a wide concentration range was revealed (Table I).

Results allowed the authors to justifiably conclude that capillary lactate accurately predicts arterial lactate, and therefore capillary blood can be used to determine lactate in the neonate.

Capillary blood lactate measured by hand-held monitors

Although the above study [1] provides evidence to suggest that capillary blood could be used in lieu of arterial blood, it is, apparently, quite unique in its design in that the method of analysis used for both capillary and arterial lactate estimation was the same well-validated method (a blood gas analyzer in this case).

All other recent studies [2-7] examining the validity of using capillary blood as an alternative to arterial blood are really addressing a specific issue: the clinical applicability of hand-held lactate monitors. Clinical interest in capillary blood lactate measurement has been driven by the availability of a range of these highly portable (hand-held) lactate instruments that are designed for rapid measurement of lactate concentration in capillary blood.

They were originally developed for sports medicine research, having established application both in the sports physiology laboratory, and the field [8]. Most of these hand-held analyzers (there are at least six) employ essentially the same method of lactate measurement: enzymatic amperometry (EA); less commonly, enzyme-mediated reflectance photometry (ERP) is employed.

The enzyme lactic oxidase, present on the analyzer sensor/test strip, reacts with lactate in the sample and the products of this reaction cause a measurable current change (EA) or color intensity change (ERP) proportional to concentration of lactate in the measured sample.

Sample volume required is very small, typically less than 50 μL and in several cases <1 μL. Analysis time of most of these instruments is <60 seconds (range 10-280 seconds) [8]. They are easy to use, simply requiring the operator to apply an unmeasured small drop of capillary blood, obtained by fingerstick or earlobe puncture, to the sensor/test strip of the analyzer.

These hand-held instruments may be suitable for rapid bedside lactate measurement by clinical (non-laboratory) staff in a prehospital [9] or emergency room setting [10]. Rapid lactate measurement is clinically desirable, particularly for early assessment and prognostication (triage) of those suspected of suffering sepsis/septic shock.

Lactate ≥2.0 mmol/L is a criterion for diagnosis of septic shock [11] and every hour of delay in treatment of septic shock is associated with increased mortality [12]. Rapid lactate measurement may also be clinically helpful for monitoring lactate clearance among the generality of intensive care patients with raised lactate, including those being resuscitated from septic shock [13].

Patients who are suspected of suffering sepsis/septic shock as well as those with confirmed sepsis/septic shock are the focus of most of these studies [2-7] seeking to examine the relationship between capillary and arterial lactate concentration.

Comparing arterial and capillary lactate – study design

In essence all these studies [2-7] have a common and simple design based on the assumption that arterial blood is the gold standard "reference" sample. Lactate concentration of capillary blood is compared with lactate concentration of arterial blood collected from the same patient at the same time, among a defined cohort of intensive care or emergency room patients.

The subjects of one study [7] are not human patients but pigs exposed to experimentally induced hyperlactatemia. By contrast with the study by Fauchere et al [1] in which both capillary and arterial blood lactate concentrations were determined by the same method, all but one of these studies [2-7] involve two methods: capillary lactate is determined by a hand-held lactate analyzer, and arterial lactate (the reference measurement) is determined by a well-validated point-of-care or central laboratory method.

The exceptional study [6] employed a hand-held lactate monitor to measure both capillary and arterial lactate, although in common with all other studies, a "reference" central laboratory method was also used to determine lactate concentration of the arterial samples.

Other important differences in detail between these studies are highlighted in Table II.

One of four hand-held lactate analyzers (analyzer A, B, C or D) was used in these studies. Analyzers A, B and D employ the same methodology: enzymatic amperometry (EA), whilst analyzer C employs enzyme-mediated reflectance photometry (ERP).

The single animal study [7] involved comparing capillary and arterial blood concentration of five pigs before, and during experimentally induced hemorrhagic shock. Progressive blood loss was performed on these pigs in order to achieve a severe reduction in blood pressure (40 mmHg) consistent with clinical shock; inevitably this blood loss (hypovolemia) caused reduced tissue perfusion and consequent tissue hypoxia with progressive rise in blood lactate.

Study date [Ref]	Number and type of patients studied	Capillary lactate method	Reference Arterial lactate method	Number of paired (capillary/arterial) samples	Time between sampling capillary and arterial blood
2016 [2]	37 adult ICU patients in shock (57% septic shock)	Hand-held analyzer A EA	Standard enzyme laboratory method	139	"simultaneous"
2013 [3]	79 adult ER patients with signs of tissue hypoperfusion, i.e. shock	Hand-held analyzer B ERP	Blood gas analyzer	79	"simultaneous"
2016 [4]	40 adult surgical ICU patients (62% in shock)	Hand-held analyzer C EA	Two analyzers used: point-of-care blood gas analyzer AND standard enzyme laboratory method	61	<10 mins
2011 [5]	30 adult ICU patients with septic shock	Hand-held analyzer B ERP	Standard enzyme laboratory method	30	"At the same time"
2015 [6]	117 adult ER patients with signs of sepsis (63% severe sepsis)	Hand-held analyzer D EA *Note: both capillary and arterial blood measured with this instrument*	Standard enzyme laboratory method	117	Average time 19 ± 2 mins
2010 [7]	Animal study (five pigs with induced hemorrhagic shock)	Hand-held analyzer A EA	Blood gas analyzer at the "point of care"	20	"At the same time"

TABLE II: Detail of six recent studies comparing capillary and arterial lactate

Comparing arterial and capillary lactate – study results

There is commonality among most of these studies [2, 4, 5-7] in the way the primary data (paired arterial and capillary lactate concentrations) are statistically manipulated and presented. Correlation between arterial and capillary values is determined by linear regression with generation of correlation coefficient r or r^2.

In addition, Bland-Altman analysis is used to determine level of agreement between capillary and arterial values. This allows generation of mean difference (bias) and 95% limits of agreement which defines the precision of the bias. Results of these statistical analyses for the five studies are presented in Table III.

Best evidence of agreement between capillary and arterial lactate is provided by the results of

Study date [Ref] No of pairs	Approximate range of lactate concentration (mmol/L)	Mean difference/ bias capillary minus arterial (mmol/L)	95% limits of agreement (mmol/L)	Correlation r, r (p-value)
2016 [2] 139 pairs	<0.5 to 22.0	0.6	−3.7 to 4.9	r^2=0.85
2016 [4] 61 pairs	0.8 to 14.0	0.99	−3.3 to 1.3	r=0.94 (p <0.001)
2011 [5] 30 pairs	1.1 to 15.0	1.32	−0.9 to 3.5	r=0.94 (p = 0.01)
2015 [6] 117 pairs	0.5 to 13.0	0.98 *Note: both capillary and arterial blood measured on hand-held analyzer*	Not recorded	r=0.82 (p <0.001)
2010 [7] 20 pairs	1.0 to 16.0	−0.115	−0.99 to 0.76	r=0.99

TABLE III: Study results (regression and Bland-Altman analysis)

	Object of employing ROC curve analysis	Results of ROC curve analysis
Seoane L *et al* [3]	To determine a cut-off value for capillary lactate that predicts reference arterial lactate 2.0 mmol/L with best sensitivity/ specificity	Area Under Curve (AUC) 82% (95% CI 78-94) Capillary lactate 2.35 mmol/L predicts arterial lactate 2.00 mmol/L with sensitivity of 81% (95% CI 60-90) specificity of 70% (95% CI 53-83)
Contenti J *et al* [6]	To compare the effectiveness of arterial lactate and capillary lactate (both determined by hand-held analyzer) to identify patients with severe sepsis at ER triage.	Area Under Curve (AUC): Arterial lactate: 0.759 ± 0.047 (p<0.01) Capillary lactate: 0.747 ± 0.048 (p<0.01)

TABLE IV: Study results (ROC curve analysis)

the animal study [7] which reveals near-perfect correlation and excellent agreement (mean bias just 0.015 mmol/L).

In general, patient studies reveal good correlation but marked bias, capillary lactate concentration tending to be higher than arterial blood concentration. The wide 95% limits of agreement (−3.7 to 4.9 mmol/L) revealed by one study [2] suggest particularly poor level of agreement, despite relatively low mean difference/bias (0.6 mmol/L).

In subset analysis of their data Sabat *et al* [4] demonstrated better correlation and agreement in patients not receiving vasopressor drugs compared with those who were on vasopressors (correlation r=0.96 versus 0.92; and mean bias: 0.51 mmol/L versus 1.28 mmol/L).

Uniquely among the studies discussed here, Sabat et al [4] also reported capillary and arterial lactate levels trending over time in individual patients (n=12) during resuscitation from septic and hemorrhagic shock. They show graphically that capillary and arterial trend closely over time: rising, peaking and falling in tandem. They report "significant deviations between capillary and arterial lactate were rare".

The authors of two studies [3, 6] employed receiver operating characteristic (ROC) curve analysis of their primary data (paired capillary and arterial lactate). The object and result of ROC curve analysis is presented in Table IV.

ROC curve analysis by Seoane et al [3] confirms the bias between capillary and arterial lactate (capillary > arterial) and suggests that if capillary blood is used to help identify patients with septic shock, the most appropriate lactate cut-off value is 2.35 mmol/L rather than 2.00 mmol/L.

ROC curve analysis by Contenti et al indicates arterial lactate (determined by hand-held analyzer) was (marginally) more effective than capillary lactate (determined by hand-held analyzer) in the early identification of severe sepsis among their study cohort of ER patients.

Is the level of disagreement revealed by these studies clinically significant?

None of the studies define acceptable level of agreement a priori so it is difficult to interpret the clinical significance of the bias (capillary > arterial) evident in all patient studies and the variable limits of agreement.

Clearly evidence suggests that the use of capillary blood measurement is associated with risk of overtriaging patients with suspected septic shock if the recommended cut-off value (2.0 mmol/L) is used.

In general, the authors of these studies conclude that the level of disagreement they find is not sufficient to proscribe the use of capillary lactate for diagnosis/assessment of sepsis/septic shock. Enthusiasm is tempered, however, and the reflected general view is that capillary blood lactate should be reserved for clinical settings where rapid measurement is necessary and rapid arterial lactate measurement is not available.

For example, Collange et al [2] conclude that "measurement of capillary lactate […] is a simple and fast bedside technique that has fair performance for a screening strategy before arterial blood measurement can be obtained. Patients with elevated capillary lactate or in shock should be monitored with atrial-based lactate".

Summary

- A single study of sick neonates indicates capillary blood lactate accurately reflects arterial blood lactate. There seems a paucity of published evidence to support the findings of this study.

- All other published studies examining the relationship between capillary and arterial lactate are designed to answer the limited but clinically relevant question: does capillary lactate (measured by hand-held device) accurately reflect arterial lactate (measured by well-validated standard methods)?

- These studies focus almost exclusively on patients with suspected sepsis/shock or patients being resuscitated from septic shock, so they only provide limited information about the relationship between capillary and arterial lactate in healthy individuals and the generality of patients who require lactate testing.

- In general, these studies demonstrate good correlation between capillary and arterial lactate but imperfect agreement; all studies

reveal a significant bias, with capillary blood lactate tending to be higher than arterial blood. The magnitude of this bias varies between studies (from –0.11 mmol/L to 1.32 mmol/L) as do 95% limits of agreement.

- Given the bias and variable level of agreement revealed by these studies, it cannot be claimed that capillary lactate measured by hand-held lactate devices accurately reflects arterial lactate measured by standard, well-validated point-of-care and central laboratory methods.

- Capillary blood lactate measurement should be used with caution and reserved for clinical settings that do not allow sufficiently rapid arterial lactate measurement.

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